DOI:10.1111/j.1365-2125.2004.02209.x

Comparison of tincture of opium and methadone to control opioid withdrawal in a Thai treatment centre

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Keywords
methadone, opioid withdrawal, Thailand, tincture of opium

Received
4 November 2003
Accepted
21 April 2004

Aims
To evaluate the effectiveness of oral tincture of opium (TOP) and methadone to control opioid withdrawal in patients in northern Thailand.

Methods
Open label, parallel group study in an inpatient facility compared 15 former heroin users receiving methadone 5–20 mg 12 hourly with 15 former opium smokers receiving TOP (3.33–10 mg morphine equivalents 12 hourly). At 0, 1, 3 and 8 h, blood, withdrawal scores and subjective opioid effects were collected.

Results
There was a reciprocal association between withdrawal scores/direct subjective opioid effects and plasma (R)-methadone, but not plasma morphine, concentrations. Withdrawal scores at the time of dosing were higher in the TOP patients (9.1 ± 3) than in the methadone patients (4.5 ± 4.6) and in the TOP patients were significantly (P = 0.001) attenuated at 3 and 8 h.

Conclusions
At the doses used, TOP was inferior to methadone in suppressing withdrawal. It could prove to be a cost effective and valuable drug, but only after dose size and frequency are further investigated.

Introduction

The physical manifestations of dependence resulting from the repeated use of opium, one of its active components (such as morphine or codeine) or their derivatives (such as heroin) or synthetic opioids, appear to be virtually identical. Withdrawal signs and symptoms can play a major role in the ongoing use of these drugs.

Whilst heroin dependence is a major and increasing problem in developed societies, this is also the case in many developing and transitional economy countries. In some of these countries, traditional smoking of opium continues to be the primary mode of opioid use. However, heroin administered intravenously or smoked is becoming more common [1, 2].

Methadone maintenance continues to be the main pharmacotherapy for opioid dependence in many countries as it satisfies the criteria for a successful substitution program [3–5]. In some countries, however, the cost of the drug is a barrier to its widespread use. One response to this has been the use of tincture of opium

as substitution treatment. This is an extemporaneous preparation of opium in alcohol and water, that in pharmaceutical preparations, is standardized to contain 1% morphine. It appears to be a more culturally acceptable alternative to drugs such as methadone in some parts of South-East Asia since it is perceived as a traditional medicine.

Auriacombe and coworkers [6] reported that body weight and scores for physical and psychological health, socioprofessional status and family relationships improved significantly after 14 months of 10–15 g day^{-1} of opium tincture in six opium-dependent subjects. There are no reports of the effectiveness or side-effects of tincture of opium compared with methadone.

The aim of this study was to examine the effectiveness of tincture of opium and methadone for treatment of opioid withdrawal using the locally accepted dosing regimens in the setting where such treatment is carried out.

Methods

This open label study was approved by the Research Ethics Committee of the Royal Adelaide Hospital (Adelaide, Australia) and the Thai Ministry of Public Health (Bangkok, Thailand).

Subjects and protocol

All subjects freely agreed to participate in this study after the procedures were fully explained. Consent was given verbally, since not all subjects were literate. All subjects were inpatients at the Northern Drug Dependence Treatment Centre, Chiang Mai, Thailand. Fifteen subjects were recruited in each of the two treatment groups. The methadone group (14 male/1 female) had 0.25–20 (median 10) years history of intravenous heroin use, with ages and body weights ranging 19–54 (mean 34) years and 43–88 (mean 57) kg, respectively. Each was administered (R)-methadone orally as a liquid formulation containing 10 mg ml^{-1} methadone HCl in syrup with small amounts of tartrazine and lemon oil for colouration and odour, respectively, and 9% ethanol (1 subject 5 mg, 5 subjects 10 mg, 4 subjects 15 mg, 5 subjects 20 mg) every 12 h. The tincture of opium patients were all males with ages and body weights ranging 20–51 (mean 35) years and 42–52 (mean 48) kg, respectively, and had a 2–20 (median 10) years history of opium smoking. Each was administered a tincture of opium (formulated as Tincture Gential Co. 6 ml, Berberies Extract 6 ml, Tincture of Opium 6 ml (containing 1% anhydrous morphine), Peppermint Spirit 1.8 ml and purified water to 90 ml) orally (4 subjects as 3.33 mg morphine equivalents, 10 subjects as 6.66 mg morphine equivalents, 1 subject as 10 mg morphine equivalents) every 12 h. This mixture contained 10 mg of anhydrous morphine in 15 ml. Both liquid formulations were produced by the Quality Assurance Department of the Government Pharmaceutical Organization, Bangkok, Thailand. Certificates of analyses were obtained verifying the concentrations of opioids by HPLC within 5% of the required specifications.

All patients had received a minimum of 4 days' treatment of either methadone or tincture of opium at their constant dose prior to being studied. Each patient's dosage of either methadone or tincture of opium was based on their reported heroin or opium usage and are those usually employed in this centre. Patients known to be HIV positive, pregnant or breastfeeding were excluded.

Each patient was studied for 8 h during the 12 h interdosing interval. The following were carried out at 0, 1, 3 and 8 h after dosing: collection of a 10 ml venous blood sample; measurement of heart rate (radial pulse palpation), blood pressure (sphygmomanometer), body temperature, and respiration rate (direct observation); recording of self-reported opioid effects and opioid withdrawal symptoms [7]. Sixteen symptoms characteristic of opioid withdrawal were recorded as present or absent to give a score from 0 to 16 (0 = no withdrawal; 16 = maximum withdrawal). For opioid effects, patients were asked to rate intensity of drug effect and experience of 'high/liking' on a scale from 0 to 4 (0 = no effect; 4 = maximal effect).

The blood samples were centrifuged and the plasma was stored at –20 °C until completion of the clinical arm of the study. The plasma samples (on dry ice) and raw data were air freighted to the Department of Clinical and Experimental Pharmacology, University of Adelaide for analysis.

Analytical methods

Plasma samples were analyzed using HPLC for either morphine [8] or (R)-methadone [9]. Both assays were accurate and reproducible and quality control samples were used throughout each analytical run for each analyte: morphine (20 and 2 ng ml^{-1}); (R)-methadone (269, 112 and 27 ng ml^{-1}). For morphine, interassay inaccuracy and imprecision of QC samples were <13%, while for (R)-methadone this was <7%. The lower limit of quantification (LLOQ) for morphine was 0.5 ng ml^{-1} and for (R)-methadone 15 ng ml^{-1}. Samples were assayed within 11 and 16 months of collection for morphine and methadone, respectively, being stable in plasma at –20 °C over this time period [10, 11].

Statistical analysis

Statistically significant changes in plasma drug concentrations, withdrawal score, high/liking score and drug effect score over the four blood collection/observation times were assessed using the SPSS procedure GLM: Repeated Measures with Greenhouse-Geisser adjustment where the assumption of sphericity could not be met (SPSS™ SPSS Inc. Chicago, Illinois). In order to assess significant changes in comparison with zero time measurement, a model was specified for within-subject contrasts that compared the initial measurement with each subsequent measurement. All data are reported as mean ± SEM [range].

Results

Results for the two groups are presented in Figures 1 (tincture of opium) and 2 (methadone).

Plasma concentrations

For the methadone treated patients, plasma morphine concentrations at time zero were below the LLOQ in 12 patients and in the remaining three patients were <1 ng ml^{-1}. For the tincture of opium treated patients, the time zero samples contained substantial concentrations (mean, range) of morphine (12, 1–20 ng ml^{-1}) and were similar to the 1 h sample (12, 7–19 ng ml^{-1}). Plasma morphine concentrations then declined rapidly such that at 8 h they were 2.5 [range 1.1–5.6] ng ml^{-1} (Figure 1). Plasma morphine concentrations showed significant changes over time ($F = 26.0$ with Greenhouse-Geisser adjustment, $P < 0.001$), specifically between zero and 3 ($P = 0.012$) and 8 ($P < 0.001$) h. The peak concentration of (R)-methadone was 85 (range 28–182) ng ml^{-1} (Figure 2).

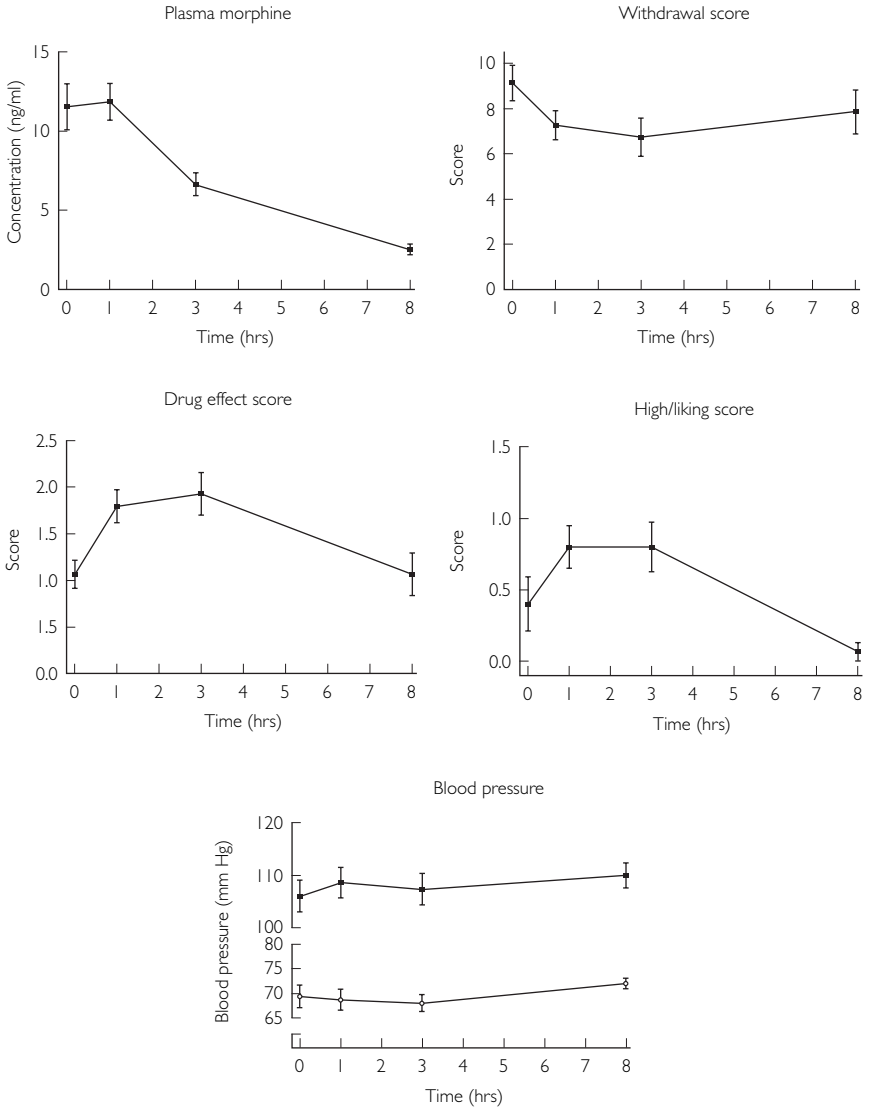

Figure 1

Measurements during part of one dosing interval in 15 Thai patients taking tincture of opium every 12 h (four subjects as 3.33 mg, 10 subjects as 6.66 mg, one subject as 10 mg, morphine equivalents). All values are mean ± SEM. Systolic (■), diastolic (○)

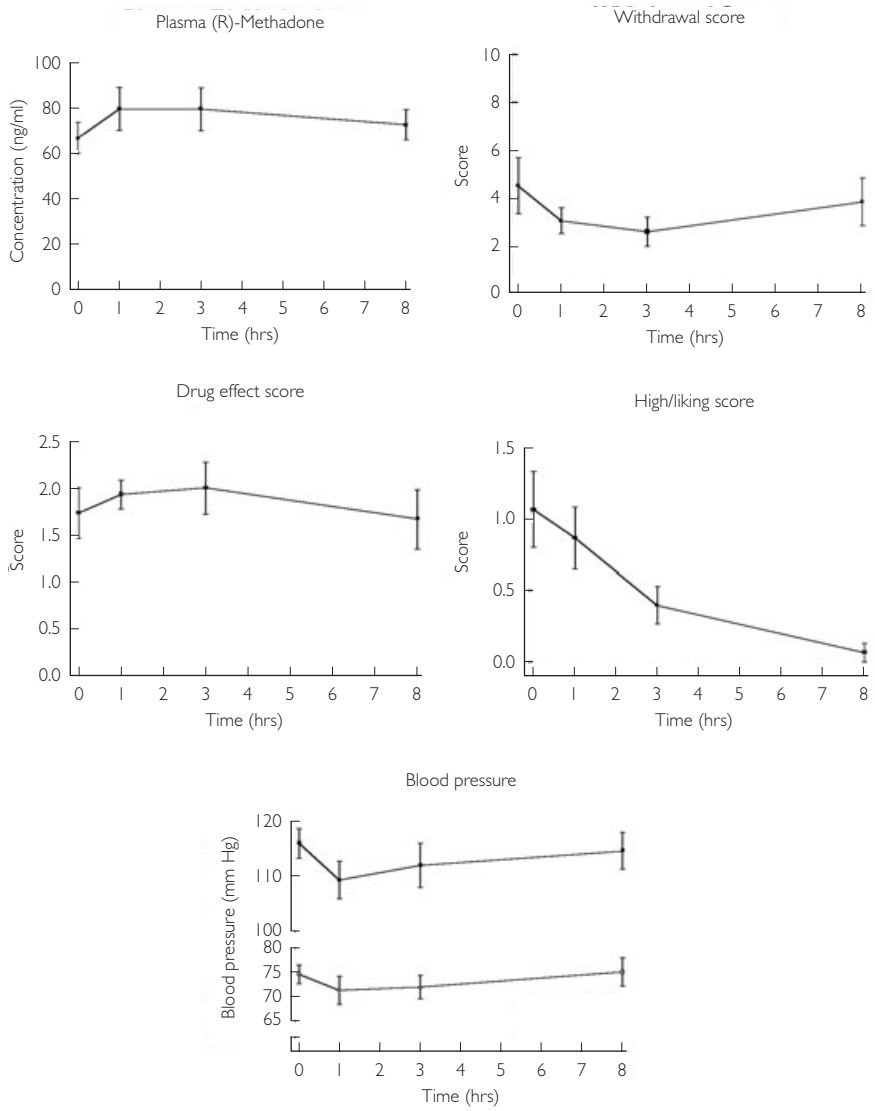

Figure 2
Measurements during part of one dosing interval in 15 Thai patients taking (R)-methadone every 12 h (one subject 5 mg, five subjects 10 mg, four subjects 15 mg and five subjects 20 mg). All values are mean ± SEM. Systolic (■), diastolic (○)

Self-report measures

For both groups, the time courses of withdrawal and drug effect/high/liking scores were inversely associated (Figures 1 and 2). Withdrawal scores were maximal (9.1 ± 3.0 in the tincture of opium patients; 4.5 ± 4.6 in the methadone patients) at the time of dosing and substantially lower 3 h later. For the tincture of opium patients, withdrawal scores showed significant changes over time ($F = 4.02$, $P = 0.013$). The differences were between 0 and 1 h ($P = 0.001$) and 3 h ($P = 0.008$). For the methadone patients, there was no statistically significant ($P = 0.067$) change over time for withdrawal scores, but high/liking scores showed significant changes over time ($F = 7.67$, $P = 0.001$). The differences were between 0 and 3 h ($P = 0.036$) and 8 ($P = 0.002$) h. Withdrawal scores appeared higher amongst the tincture of opium treated patients at each time point compared to the methadone treated patients.

For tincture of opium treated patients, the drug effect scores showed significant changes over time ($F = 10.74$, $P < 0.001$), specifically between 0 and 1 ($P < 0.001$) and 3 ($P < 0.001$) h (Figure 1). There was no similar change for the methadone patients. Scores of high/liking were low for both methadone (Figure 2) and tincture of opium (Figure 1) patients. In the latter group, the high/liking score showed significant changes over time ($F = 6.04$, $P = 0.002$), but only between 0 and 1 h ($P = 0.028$).

Objective measures

In both groups, there were no significant ($P > 0.05$) changes over time for any objective measure.

Discussion

The primary objectives of substitution treatment for opioid dependent individuals are reduction/cessation of illicit drug use and social rehabilitation of the user. These objectives are achievable with methadone, buprenorphine and levo-alpha-acetylmethadol (LAAM) [12] and more recently with controlled-release morphine [13]. The choice of drug should be governed by the risk- and cost-benefit analyses for the individual and the society in which the treatment is available. Local cultural attitudes and drug affordability are likely to play an important role in determining the acceptance and success of any treatment. Tincture of opium could be a suitable substitution treatment but, to our knowledge, it has not been formally evaluated in the relevant patient population. It was appropriate therefore to explore the effectiveness of tincture of opium and to compare it with methadone in a setting and at dosing regimens which are orthodox in this therapeutic milieu. We acknowledge that there are several limitations to this study: the short duration of the study; the absence of formal dose escalation to achieve a desired end-point; the open label design and differences in the control group with respect to their illicit opioid use. These limitations stemmed from pragmatic and logistic imperatives, which dictated what was acceptable to the patients.

Methadone was effective in controlling withdrawal from intravenous heroin use in these patients, who showed relatively low withdrawal scores and premethadone dosing plasma morphine concentrations <1 ng ml^{-1}. The measurement of predose plasma morphine concentrations serves as a marker of illicit heroin (or tincture of opium) use, analogous to the assay of opioids in urine. In the methadone subjects, the low plasma morphine concentrations confirmed the efficacy of methadone. Withdrawal suppression appeared to be related to the time course of plasma (R)-methadone (the active enantiomer) concentrations over time, which has been previously reported in Caucasian methadone maintenance patients [14, 15].

We did not consider it appropriate to perform formal statistical analyses to compare outcomes between the two groups, since patients in one group were intravenous heroin users and in the other group opium smokers. Nevertheless, there were several differences between the two cohorts. First, withdrawal appeared to be less well controlled in the tincture of opium group, as evidenced by higher withdrawal scores and the presence of clinically significant concentrations of morphine in the predose plasma samples in many of the patients. We cannot readily explain the presence of such concentrations of morphine in the predose samples in this group as the treatment clinic staff confirmed that the zero hour sample was that sample just prior to the next dose. Second, whilst there were significant time-related subjective (withdrawal, drug effect, high/liking) effects, these changes were not reflected in the changes in plasma morphine concentrations, which declined from a peak at the time of dosing. Thus, whilst drug effects were demonstrable, the results suggest that another alkaloid other than morphine may be responsible for the actions of tincture of opium. There were, however, some similarities between the two groups. The duration of drug effect was similar and high/liking scores were low over the observation periods.

We conclude that methadone was effective in controlling withdrawal from intravenous heroin use in these patients, as previously reported in Caucasian patients [14]. Whilst there was an observable drug effect with tincture of opium in the opium smokers, it was inadequate to satisfactorily suppress withdrawal, probably because the commonly prescribed doses and the resulting plasma morphine concentrations were too low. Nevertheless, as a culturally acceptable alternative to methadone, it may be a useful and possibly more cost-effective drug, but only after dose size and dosing frequency have been adequately investigated.

This study was supported by the Commonwealth Department of Health (Canberra, Australia) and the National Health and Medical Research Council of Australia (grant number 990586). We thank Andrew Menelaou for assaying plasma samples, Paul Christie for statistical assistance, and the staff and patients of the Northern Drug Dependence Centre, Chiang Mai Province, Thailand for their assistance and co-operation. This study was presented in part at the 8th South-East Asian-Western Pacific Regional Meeting of Pharmacologists (Taipei, Taiwan) November 1–5, 1999.

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